

**REMARKS**

35 U.S.C. § 103(a) – Obviousness

The Examiner rejects all pending claims under 35 U.S.C. § 103(a) as obvious over Shoshan (WO0210449) in view of Bennett (US 6172216) and Wengel. The Examiner asserts that Shoshan discloses a 65 base oligonucleotide, SEQ ID NO: 28264, which “is disclosed as an RNA transcript or splice variant of a transcript (see ¶[0115]),” and to which “SEQ ID NO:19 of the instant invention is 100% complementary.” *Office Action* at 3. The Examiner also asserts that Shoshan “teach that these RNA transcripts can be used as the basis for designing antisense RNA and siRNA. (see ¶ [0111] through [0113]).” *Id.* The Examiner asserts that it would be obvious to make antisense to SEQ ID NO: 28264 based on Shoshan, and that the modifications and pharmaceutical compositions recited in the claims are obvious in view of Bennett. Applicants respectfully traverse.

Applicants note that the sequence reproduced in the Office Action on page 3 is SEQ ID NO: 28624, not SEQ ID NO: 28264 as stated in the Office Action. In addition, Applicants note that the Examiner cites to paragraph numbers in the Shoshan reference even though it does not contain any paragraph numbers. Applicants assume that the Examiner is referring to the paragraph numbers found in US 2003/0165843, which lists the same inventors as WO0210449 and appears to be the same disclosure as US 2003/0165843. However, as US 2003/0165843 was not cited in the rejection, Applicants will refer instead to the disclosure of WO0210449.

The Examiner admits that while Shoshan teaches that the disclosed transcripts can be the basis for designing antisense RNA and siRNA, “Shoshan et al. does not describe an antisense oligonucleotide o[f] 12 to 50 nucleotides in length targeting the disclosed sequence having the sequence of SEQ ID NO: 19 a[s] recited in the instant claims.” *Office Action* at 3. To overcome this deficiency in the reference, the Examiner argues that “although Shoshan et al. discloses a plurality of oligonucleotide RNA transcripts, the disclosure of this reference clearly suggests designing antisense and siRNA oligonucleotides targeting these sequences. Therefore, although the number of transcripts is numerous, nonetheless the sequence of these oligonucleotide RNA transcripts are disclosed.” *Office Action* at 5.

Applicants respectfully submit that the disclosures regarding antisense in Shoshan are generic in nature, and do not suggest designing antisense to any particular oligonucleotide of the

invention, or specifically to SEQ ID NO:28624. Instead, Shoshan makes a generic disclosure that “[b]ecause the oligonucleotides of the present invention are able to bind to one or more splice variants of the transcriptome, these oligonucleotides have uses in *in situ* and *in vivo* antisense contexts.” WO0210449 at 27, lines 10-12 (emphasis added). Similarly, Shoshan states that using known techniques, “an antisense RNA based upon the oligonucleotides of the present invention can be employed to inhibit or prevent translation of an mRNA at the cellular level.” *Id.* at lines 20-23 (emphasis added). Shoshan offers no reason to select SEQ ID NO: 28624 out of the 32,337 sequences disclosed. In fact, Shoshan does not mention SEQ ID NO: 28624 or any other SEQ ID NO. anywhere in the specification of WO0210449, outside of the sequence listing.

Thus, at best, Shoshan discloses a genus of antisense based on “the oligonucleotides of the present invention.” This genus includes antisense to at least the 32,337 transcript sequences disclosed by Shoshan for human, rat and mouse, although Shoshan contemplates oligonucleotide libraries to other species. *See id.* at 30, lines 7-10. Each of the 32,337 disclosed sequences are 60 or 65 bases in length. Considering only antisense oligonucleotides that are 20 bases in length, as suggested by the Examiner in the Office Action, there are about 40 or 45 antisense oligonucleotides for each of the 32,337 disclosed transcripts. This represents a genus of approximately 1.3 to 1.5 million antisense oligonucleotides. If all of the sizes of antisense and possible modifications disclosed by Shoshan and Bennett are considered, as well as transcripts from other species, the size of the disclosed genus of antisense is practically infinite.

Where a cited reference discloses a genus, the Examiner should follow the three step obviousness analysis laid out in the M.P.E.P. §2144.08: (1) determine the scope and content of the prior art, including the size of the disclosed genus; (2) determine the differences between the closest expressly described prior art species or subgenus and the claimed species or subgenus; and (3) determine the level of skill in the art. Based on the findings related to these three factors, the Examiner must then determine “whether it would have been obvious to one of ordinary skill in the relevant art to make the claimed invention as a whole, i.e., to select the claimed species or subgenus from the disclosed prior art genus.” *Id.* (emphasis added).

The Examiner has failed to provide any reason why one of skill in the art would find it obvious to select the antisense oligonucleotides of the pending claims out of the at least 1.3

million member genus disclosed in Shoshan. As mentioned above, Shoshan does not provide any reason to select SEQ ID NO: 28624, which is not even mentioned in the specification.

The Examiner's arguments based on the small size of SEQ ID NO: 28624, and the preferred 20 nucleobase size of Bennett are also flawed. The Examiner's statement that "the sequence of SEQ ID NO: 19 of the instant invention could be immediately envisioned" presupposes that one of skill in the art would select the subgenus of SEQ ID NO: 28624 from the 32,337 transcripts disclosed in Shoshan. The Examiner has not provided any reason one of skill in the art would select this particular sequence to use as the basis for making antisense, and Shoshan does not provide any such basis.

If the Examiner is arguing that the pending claims are obvious because antisense having SEQ ID NO: 19 are encompassed by the genus of antisense disclosed in Shoshan, this argument also fails. The M.P.E.P. and relevant case law have clearly rejected this reasoning as a sufficient basis for establishing a *prima facie* case of obviousness:

The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious."); *In re Jones*, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992) (Federal Circuit has "decline[d] to extract from *Merck [& Co. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir. 1989)] the rule that... regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it."). See also *In re Deuel*, 51 F.3d 1552, 1559, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995).

M.P.E.P. § 2144.08 (emphasis added).

In sum, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness because there is no basis to select the claimed antisense oligonucleotides from a genus comprising at least 1.3 million species. Similarly, the Examiner has provided no basis for selecting the subgenus of SEQ ID NO: 28624 from the 32,337 disclosed transcripts in Shoshan. Mere disclosure of a genus which encompasses a claimed species or subgenus is not sufficient to establish obviousness. This is particularly true where the genus encompasses at least 1.3 million species or 32,337 subgenus. See M.P.E.P. § 2144.08.II.A.4(a). Neither of Bennett or Wengel overcome this shortcoming, as the Examiner has not pointed to any portion of either reference

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which would provide a basis for selecting the claimed compounds from the disclosed genus of Shoshan.

Finally, even if the Examiner has established a *prima facie* case of obviousness, which Applicants do not concede, Applicants note that in Example 15, Table 1, of the instant specification, SEQ ID NO: 19 shows 79% inhibition of Human Growth Hormone Receptor expression *in vitro*. This result is clearly unexpected in view of the cited references which do not disclose any information regarding SEQ ID NO: 28624, including whether SEQ ID NO: 28624 represents a portion of the transcript accessible to antisense molecules *in vitro*. Given that any *prima facie* case of obviousness is extremely weak, this unexpected property is more than sufficient to overcome it.

For at least the above reasons, Applicants request reconsideration and withdrawal of the rejection of the pending claims as obvious over Shoshan in view of Bennett and Wengel.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Patents/Applications

Applicants wish to draw the Examiner's attention to the following patents/applications. Applicants encourage the Examiner to review and monitor the prosecution of the following patents/applications throughout the pendency of this application.

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Serial Number	Title	Filed
10/927,466	MODULATION OF GROWTH HORMONE RECEPTOR EXPRESSION AND INSULIN-LIKE GROWTH FACTOR EXPRESSION	08/25/2004
10/547239	MODULATION OF GROWTH HORMONE RECEPTOR EXPRESSION AND INSULIN-LIKE GROWTH FACTOR EXPRESSION	08/25/2005

CONCLUSION

Applicants submit that the present application is in condition for allowance and respectfully requests an action to that effect. If any issues remain, the Examiner is invited to contact Applicants' counsel at the number provided below in order to resolve such issues promptly. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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